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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/244,195	02/04/1999	GEORGE BARRIE KITTO	D6073	3475

27851 7590 06/02/2004

BENJAMIN A. ADLER
8011 CANDLE LANE
HOUSTON, TX 77071

EXAMINER
PARKIN, JEFFREY S

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/244,195	KITTO ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8-10,12 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8-10,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114.

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the submission filed 05 December, 2003. Claims 1-5, 7, and 11 were canceled without prejudice or disclaimer, claim 6 amended, and new claims 12 and 13 presented. Thus, claims 6, 8-10, 12, and 13 are pending in the instant application.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability

> under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 6, 8-10, 12, and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brey *et al.* (1992), in view of Georgiou *et al.* (1994), and further in view of Haseltine *et al.* (1991), Kang (1993), and Rodman (1997). As previously set forth, Brey *et al.* (1992) describe the preparation of S. *typhimurium* expression systems (including those derived from strain SL3261) that are useful for the expression of heterologous (e.g., malaria) antigens. A detailed description of suitable expression vectors can be found in Table 1 and column 20. This publications also discloses that said expression systems are particularly useful because the vectors of interest retain their enteroinvasive properties but are markedly reduced in terms of virulence. This properties make these vectors particularly useful for generating both humoral and cell-mediated immune responses against the antigen of interest (see col. 7, first paragraph). Various vaccine formulations can be prepared and routes of administration utilized (i.e., oral, intradermal, intramuscular, intraperitoneal, intranasal, etc.) (see col. 21,

section 5.6). A particularly attractive feature of this vector system is the ability of S. *typhimurium* to invade the gut epithelial tissue thereby leading to strong mucosal and helper immune responses (see cols. 23 and 24, section 5.6.2). Other advantages of this vector system include the lack of a necessary purification step for the immunogen of interest and the ability of this system to be inexpensively produced and conveniently administered. The probability of adverse reactions in both animals and humans is also low. This teaching does not disclose the utilization of an Lpp-OmpA-Tat fusion protein.

Georgiou *et al.* (1994) describe the preparation of recombinant DNAs that are suitable for the expression of a heterologous antigen on the external surface of an enteric microorganism (e.g., E. *coli* or Salmonella). DNA constructs were prepared that were capable of encoding fusion proteins comprising the Lpp signal sequence, OmpA coding portion, and a heterologous antigen (i.e., see cols. 3, 4, 15, and Figure 1). The inventors noted that targeting sequences (e.g., Lpp) and membrane traversing amino acid sequences (e.g., OmpA) are well-known in the prior art (see cols. 3 and 4). The inclusion of these coding sequences in a fusion construct facilitates the expression, transport, and presentation of a heterologous antigen on the cell surface of a gram-negative bacterium. It was reported that various strains of Salmonella would prove particularly useful for the invention (see col. 5, last paragraph). This teaching does not disclose recombinants expressing the HIV-1 *tat* gene.

Haseltine *et al.* (1991), Kang (1993), and Rodman (1997) all provide the complete nucleotide/amino acid sequence of the HIV-1 *tat* gene and expression vectors comprising said gene. For instance, see columns 3-7 of the Haseltine publication wherein the gene, expression vectors, and cell lines producing said protein are

described. The Kang publication describes the preparation of HIV-1 Tat-expressing recombinant baculoviruses (see col 8, first paragraph). Finally, Rodman describes the preparation of recombinant Tat and its utilization in ELISA assays (see col. 15). Thus, these teachings all illustrate that HIV-1 Tat was widely available and of obvious diagnostic and medical importance.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express the HIV-1 *tat* gene provided by Haseltine *et al.* (1991), Kang (1993), or Rodman (1997), as an Lpp-OmpA-Tat fusion protein, as suggested by Georgiou *et al.* (1994), in the S. *typhimurium* expression system described by Brey *et al.* (1992), since Brey and colleagues teach that this system is useful for generating strong immune responses against the antigen of interest. The skilled artisan would have been motivated to prepare such constructs since this would facilitate the development of HIV-1 Tat-specific immunological reagents (i.e., antibodies) which can be employed in diagnostic, immunological, or biochemical assays. It would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare a fusion protein comprising the Lpp signal sequence, OmpA, and HIV-1 Tat since Georgiou *et al.* (1994) teach that Lpp-OmpA-X fusion proteins are expressed in large quantities in an antigenic/immunogenic form on the cell surface of enteric bacteria.

Response to Arguments

Applicants traverse and submit that the teachings of the prior art as they pertain to the generation of immune responses against malarial immunogens in the *Salmonella* expression system cannot be directly extrapolated to other heterologous immunogens such as HIV-1 Tat. Applicants argue that one skilled in the art could not

reasonably predict whether or not *Salmonella* expression vectors encoding HIV-1 Tat would generate strong immune responses against said immunogen. The Examiner does not concur with this assessment. The prior art clearly teaches that *Salmonella*-based expression vectors provide an efficient and facile means for delivering and expressing heterologous immunogens. Thus, both a reasonable expectation of success and sufficient motivation to employ said vehicles were present in the prior art.

Claims 6, 8-10, 12, and 13[1] are rejected under 35 U.S.C. § 103(a) as being obvious over Hone *et al.* (1996) in view of Georgiou *et al.* (1994), and further in view of Haseltine *et al.* (1991), Kang (1993), and Rodman (1997). Hone and colleagues provide attenuated *Salmonella typhimurium* vaccine vectors containing expression vectors encoding *Escherichia coli* OmpA::HIV-1 gp120 fusion proteins. These Salmonella strains induced both mucosal and

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1[1] As previously set forth, the teachings of Hone and colleagues describes the use of an S. *typhimurium* strain carrying a mutation in the *aro* locus. This attenuated bacterial strain appears to be the same strain described by Fouts *et al.* (1995, Construction and immunogenicity of *Salmonella typhimurium* vaccine vectors that express HIV-1 gp120, Vaccine, 13(17):1697-705) which was designated strain SL3261. Since the Patent Office does not have the facilities for examining and comparing applicants' claimed S. *typhimurium* strain SL3261 with the S. *typhimurium* strain employed by Hone *et al.* (1996), the burden is upon applicants to demonstrate the unobvious genotypic/phenotypic differences between the two strains. *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (C.C.P.A. 1977). *Ex parte Gray*, 10 U.S.P.Q.2d 1922 (Bd. Pat. Appl. Int. 1989).

systemic HIV-1 gp120-specific immune responses. The authors concluded (see Abstract, p. 203) that "These results, therefore, support the proposal that *Salmonella* vectors will be a safe and inexpensive means for delivery of HIV antigens to, and the elicitation of HIV-specific T cells in, the mucosal and systemic compartments." The authors also noted (p. 206, penultimate paragraph) that "It is reasonable to propose, therefore, that *Salmonella* bearing surface-expressed rgp120 will elicit gp120-specific $CD8^+$ CTLs." This teaching does not disclose Lpp-OmpA-HIV-1 Tat fusion proteins.

Georgiou *et al.* (1994) describe the preparation of recombinant DNAs that are suitable for the expression of a heterologous antigen on the external surface of an enteric microorganism (e.g., E. *coli* or Salmonella). DNA constructs were prepared that were capable of encoding fusion proteins comprising the Lpp signal sequence, OmpA coding portion, and a heterologous antigen (i.e., see cols. 3, 4, 15, and Figure 1). The inventors noted that targeting sequences (e.g., Lpp) and membrane traversing amino acid sequences (e.g., OmpA) are well-known in the prior art (see cols. 3 and 4). The inclusion of these coding sequences in a fusion construct facilitates the expression, transport, and presentation of a heterologous antigen on the cell surface of a gram-negative bacterium. It was reported that various strains of Salmonella would prove particularly useful for the invention (see col. 5, last paragraph). This teaching does not disclose recombinants expressing the HIV-1 *tat* gene.

Haseltine *et al.* (1991), Kang (1993), and Rodman (1997) all provide the complete nucleotide/amino acid sequence of the HIV-1 *tat* gene and expression vectors comprising said gene. For instance, see columns 3-7 of the Haseltine publication wherein the gene, expression vectors, and cell lines producing said protein are

described. The Kang publication describes the preparation of HIV-1 Tat-expressing recombinant baculoviruses (see col 8, first paragraph). Finally, Rodman describes the preparation of recombinant Tat and its utilization in ELISA assays (see col. 15). Thus, these teachings all illustrate that HIV-1 Tat was widely available and of obvious diagnostic and medical importance.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express the HIV-1 *tat* gene provided by Haseltine *et al.* (1991), Kang (1993), or Rodman (1997), as an Lpp-OmpA-Tat fusion protein, as suggested by Georgiou *et al.* (1994), in the S. *typhimurium* expression system described by Hone *et al.* (1996), since Hone and colleagues teach that this system is useful for generating strong immune responses against the antigen of interest. The skilled artisan would have been motivated to prepare such constructs since this would facilitate the development of HIV-1 Tat-specific immunological reagents (i.e., antibodies) which can be employed in diagnostic, immunological, or biochemical assays. It would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare a fusion protein comprising the Lpp signal sequence, OmpA, and HIV-1 Tat since Georgiou *et al.* (1994) teach that Lpp-OmpA-X fusion proteins are expressed in large quantities in an antigenic/immunogenic form on the cell surface of enteric bacteria.

Response to Arguments

Applicants proffer similar arguments to those directed at the first rejection. Applicants traverse and submit that the teachings of the prior art as they pertain to the generation of immune responses against malarial immunogens in the *Salmonella* expression system cannot be directly extrapolated to other heterologous

immunogens such as HIV-1 Tat. Applicants argue that one skilled in the art could not reasonably predict whether or not *Salmonella* expression vectors encoding HIV-1 Tat would generate strong immune responses against said immunogen. The Examiner does not concur with this assessment. The prior art clearly teaches that *Salmonella*-based expression vectors provide an efficient and facile means for delivering and expressing heterologous immunogens. Thus, both a reasonable expectation of success and sufficient motivation to employ said vehicles were present in the prior art.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (571) 272-0910 or (571) 272-0902, respectively. Direct general inquiries to the Technology Center 1600 receptionist at (571) 272-1600.

Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

30 May, 2004